

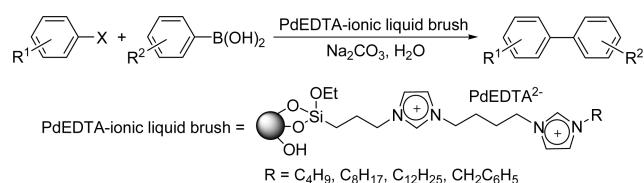
PdEDTA Held in an Ionic Liquid Brush as a Highly Efficient and Reusable Catalyst for Suzuki Reactions in Water

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An efficient and reusable catalyst with PdEDTA immobilized in an ionic liquid brush and a green procedure have been developed for coupling aryl iodides and bromides with phenylboronic acid. These reactions were conducted in water under aerobic conditions with water-insoluble or even solid aryl halides. The protocol has the advantages of excellent yields, environmental friendliness, and catalyst recyclability. There was no apparent loss of catalyst efficiency until the 10th cycle.

In recent years, the use of water as a medium for organic transformations has attracted much attention¹ due to economic and environmental concerns. Water has the advantages of low cost, nontoxicity, and nonflammability, as well as being a renewable resource.² About 80% of chemical waste has resulted from use of organic solvents.³ Most previously reported reactions in aqueous systems, even those traditionally performed in the presence of water, such as the palladium-catalyzed Suzuki–Miyaura cross-coupling

reactions,¹ were carried out with the aid of organic solvents. While the Suzuki–Miyaura reaction has become a powerful and convenient synthetic tool for the construction of C–C bonds in biaryl compounds^{4,5} and is also nowadays of great industrial significance,^{6,7} it suffers from at least one of the following shortcomings: the need for complicated and/or toxic ligands (i.e., phosphine) and organic solvent or cosolvent, and the lack of reusability. In the past decades, many efforts have been made to solve these problems through the development of active, reusable catalysts and more facile and benign procedures,^{8–10} but satisfactory solutions are still a challenge. Consequently, the development of reusable and highly efficient alternatives and environment-friendly procedures with water as the reaction medium is highly desirable.

We recently reported a series of SiO₂-supported multi-imidazolium ionic liquid brushes as a new type of catalyst that proved to be efficient for either hydrogenation of nitro aromatics or dihydroxylation of alkenes with H₂O₂.¹¹ The coral-like brush provides an ionic liquid microenvironment for catalytically active species, and has the advantage of being used in neat water. Moreover, the brush is easy to separate from reaction mixtures by simple filtration. From

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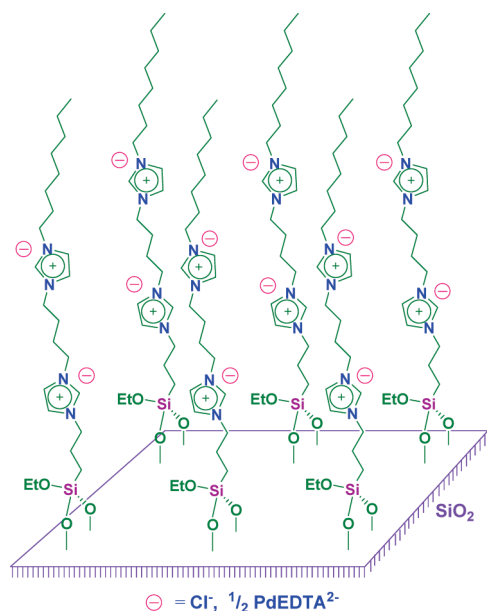


FIGURE 1. Silica-immobilized PdEDTA²⁻ ionic liquids.

the viewpoints of environmental security and economic viability, the recoverability and recyclability of such ionic liquid brushes assume great importance. The significant advantages of the brushes and a recent report by Bumagin¹² in which [PdEDTA²⁻] was proved to be an efficient catalyst for the Suzuki–Miyaura reaction motivated us to develop more efficient and environmentally friendly catalysts and procedures for this reaction. As part of our investigations of organic transformations in water, the present communication reports, for the first time, the use of a palladium-in-brush catalyst for the Suzuki–Miyaura reaction in water with excellent yields.

The PdEDTA held in SiO₂-diimidazolium ionic liquid brushes, termed SiO₂-BisILsR [PdEDTA] (Figure 1), were prepared via the ion-exchange reaction of SiO₂-immobilized diimidazolium ionic liquid brushes, SiO₂-BisILsR [Cl], with aqueous PdEDTA solution, as shown in Scheme 1.

The coupling of 4-bromoanisole and phenylboronic acid was used as a prototypical reaction for discovery of suitable reaction conditions, and examination of the activity of various catalysts. All of the reactions were carried out by stirring under reflux a mixture of the catalyst, 4-bromoanisole, phenylboronic acid, and Na₂CO₃ in ordinary (not degassed) water under aerobic conditions. No organic co-solvent, phosphine ligand, or phase transfer catalyst was required. 4-Bromoanisole was chosen as the substrate for its modest reactivity to Suzuki coupling.

The results listed in Table 1 show that the catalyst with *n*-octyl as the terminal alkyl group was the most effective for the Suzuki–Miyaura coupling reaction. For smooth reaction, 1 mol % of the catalyst was sufficient, giving the desired coupled product in nearly quantitative yield without detectable unwanted self-coupling product (entry 4). Even with an amount as small as 0.5 mol % the catalyst exhibits good performance in the reaction, affording the desired product in a yield comparable with the literature yields (entry 5).

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SCHEME 1. Preparation of Silica-Immobilized Ionic Liquid Brush Catalysts

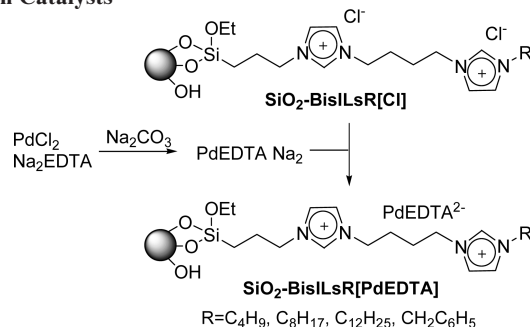
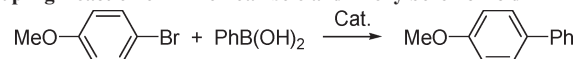


TABLE 1. The Catalytic Activity of SiO₂-BisILsR [PdEDTA] in the Coupling Reaction of 4-Bromoanisole and Phenylboronic Acid^a



entry	R in cat. (mol %) ^b (wt %) ^c	time (h)	temp (°C)	yield (%) ^d
1	<i>n</i> -Bu (2.0) (2.0)	10	100	77(5)
2	<i>n</i> -Oct (1.0) (2.0)	10	60	75
3	<i>n</i> -Oct (2.0) (2.0)	6	100	99
4	<i>n</i> -Oct (1.0) (2.0)	8	100	99
5	<i>n</i> -Oct (0.5) (2.0)	12	100	98
6	<i>n</i> -Oct (1.0) (1.0)	15	100	96
7	<i>n</i> -Oct (1.0) (0.5)	18	100	89
8	<i>n</i> -dodecyl (2.0) (2.0)	12	100	87
9	CH ₂ Ph (2.0) (2.0)	10	100	90(2)

^aConditions: 4-bromoanisole (2 mmol), phenylboronic acid (2.1 mmol), Na₂CO₃ (4 mmol), Pd catalyst, H₂O (10 mL), 100 °C. ^bThe charge of catalyst based on Pd relative to the aryl halide (number in the first set of parentheses). ^cThe Pd loading on the brush catalysts (number in the second set parentheses). ^dYield after chromatographic separation (based on aryl halide, biphenyl yields in parentheses); average of two runs.

The analogue catalysts with *n*-butyl, benzyl, or *n*-dodecyl as the terminal alkyl group were less reactive and gave the coupling products in lower yields. Moreover, small amounts of undesired self-coupling products were formed as byproducts with the *n*-butyl and benzyl catalysts. These results indicate that catalysts bearing more or less than eight carbons in the alkyl chain are less effective. The explanation may be that the octyl group is more efficient in balancing critical hydrophobic and hydrophilic parameters. Thus, it provides a suitable hydrophobic and hydrophilic environment for the aryl halides and phenylboronic acid to move into the brushes where the active catalyst attached and for the coupled product and byproduct (boronate) to move out of the brushes.

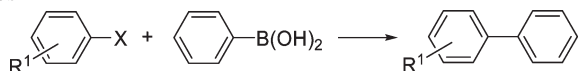
The optimal reaction temperature is 100 °C, at which the reactions were completed within 8 h with excellent yields, and no self-coupling products were observed. The reaction also worked with the *n*-octyl-terminated catalyst at lower temperature, but with lower yield (entry 2). The palladium loading is also important in the brush. The catalyst with a 2 wt % loading worked more efficiently. The catalyst with a palladium loading less than 0.5 wt % gave inferior results.

The counteranions of the catalysts had negligible influence on the reaction. Replacement of chloride with PF₆⁻, which is generally considered as the best counteranion in ionic

TABLE 2. The Recycling of SiO₂-BisILsOct[PdEDTA] (Runs 1–10) in the Coupling Reaction of *p*-Bromoanisole and Phenylboronic Acid^a

	1	2	3	4	5	6	7	8	9	10
yield ^b	99	99	99	99	99	100	96	97	98	99

^aConditions: 4-bromoanisole:phenylboronic acid:Na₂CO₃:Pd catalyst = 1:1.05:2:0.01 (mol), H₂O = 5 mL per mmol substrate, 100 °C, 8 h.
^bYields after chromatographic separation.

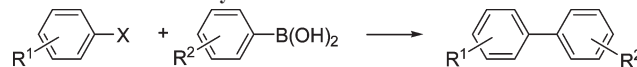
TABLE 3. Scope of the Suzuki Reaction with PdEDTA-Ionic Liquid Brush

Entry	Aryl halide	Products	Time (h)	Yield ^b (%)
1	C ₆ H ₅ Br	C ₆ H ₅ -C ₆ H ₅ (1a)	20	90
2	4-MeOC ₆ H ₄ Br	4-MeOC ₆ H ₄ -C ₆ H ₅	6	100
3	2-MeOC ₆ H ₄ Br	2-MeOC ₆ H ₄ -C ₆ H ₅	8	99
4	4-MeC ₆ H ₄ Br	4-MeC ₆ H ₄ -C ₆ H ₅	8	100
5	2-MeC ₆ H ₄ Br	2-MeC ₆ H ₄ -C ₆ H ₅	17	92
6	4-NO ₂ C ₆ H ₄ Br	4-NO ₂ C ₆ H ₄ -C ₆ H ₅	9	93
7	3-NO ₂ C ₆ H ₄ Br	3-NO ₂ C ₆ H ₄ -C ₆ H ₅	15	98
8	2-NO ₂ C ₆ H ₄ Br	2-NO ₂ C ₆ H ₄ -C ₆ H ₅	15	90
9	4-NH ₂ C ₆ H ₄ Br	4-NH ₂ C ₆ H ₄ -C ₆ H ₅	15	95
10	4-CNC ₆ H ₄ Br	4-CNC ₆ H ₄ -C ₆ H ₅	9	98
11	4-BrC ₆ H ₄ Br	4-C ₆ H ₅ C ₆ H ₄ -C ₆ H ₅	10	95 ^c
12	4-BrC ₆ H ₄ I	4-C ₆ H ₅ C ₆ H ₄ -C ₆ H ₅	20	89 ^c
13	4-BrC ₆ H ₄ I	4-BrC ₆ H ₄ -C ₆ H ₅	9	92
14			6	97
15	4-AcC ₆ H ₄ Br	4-AcC ₆ H ₄ -C ₆ H ₅		99
16	4-HO ₂ CC ₆ H ₄ Br	4-HO ₂ CC ₆ H ₄ -C ₆ H ₅	9	92 ^d
17	C ₆ H ₅ I	C ₆ H ₅ -C ₆ H ₅	10	99
18	4-MeOC ₆ H ₄ I	4-MeOC ₆ H ₄ -C ₆ H ₅	6	99
19	2-MeOC ₆ H ₄ I	2-MeOC ₆ H ₄ -C ₆ H ₅	6	99
20	4-MeC ₆ H ₄ I	4-MeC ₆ H ₄ -C ₆ H ₅	7	96
21	2-MeC ₆ H ₄ I	2-MeC ₆ H ₄ -C ₆ H ₅	11	100
22	4-NO ₂ C ₆ H ₄ I	4-NO ₂ C ₆ H ₄ -C ₆ H ₅	6	99
23	3-NO ₂ C ₆ H ₄ I	3-NO ₂ C ₆ H ₄ -C ₆ H ₅	9	98
24	2-NO ₂ C ₆ H ₄ I	2-NO ₂ C ₆ H ₄ -C ₆ H ₅	9	95
25	2-NH ₂ C ₆ H ₄ I	2-NH ₂ C ₆ H ₄ -C ₆ H ₅	5	96
26	4-CNC ₆ H ₄ I	4-CNC ₆ H ₄ -C ₆ H ₅	8	99
27	2-HOC ₆ H ₄ I	2-HOC ₆ H ₄ -C ₆ H ₅	9	92
28			9	99
29			5	98
30	C ₆ H ₅ Cl	C ₆ H ₅ -C ₆ H ₅	24	66

^aConditions: aryl halide (2 mmol), phenylboronic acid (2.1 mmol), Na₂CO₃ (4 mmol), Pd catalyst (1.0 mol %), H₂O (10 mL), 100 °C. ^bYield after chromatographic separation (based on aryl halides, biphenyl yields in parentheses). ^c2.1 equiv of phenylboronic acid was used. ^dYield after recrystallization from ethanol–water.

liquids of the imidazolium type, did not improve the reaction yields.

It is noteworthy that the palladium-in-brush catalyst can be recovered by simple filtration after extraction of the product by ethyl acetate, and recycled. Ten consecutive preparations of 4-methoxybiphenyl showed no significant reduction in yield (Table 2). In each case, the catalyst was recovered by filtration and washed with ethyl acetate and water, then the experiment repeated. ICP-MS analysis showed that after filtration of the brush the reaction stream contained only 0.96 mg L⁻¹ of Pd, i.e., 0.45% of the initial

TABLE 4. The PdEDTA-Ionic Liquid Brush-Catalyzed Suzuki Reaction with Substituted Arylboronic Acids

entry	X	R ¹	R ²	time (h)	yield ^b (%)
1	Br	H	4-MeO	7	94
2	Br	4-MeO	4-MeO	6	94
3	Br	3-NO ₂	4-MeO	5	99
4	I	4-NO ₂	4-MeO	6	99
5	Br	H	4-CF ₃	6	98
6	Br	4-Ac	4-CF ₃	7	99
7	Br	4-MeO	4-CF ₃	8	93
8	I	4-MeO	4-CF ₃	6	99
9	Br	H	4-CO ₂ H	6	88 ^c
10	Br	4-Ac	4-CO ₂ H	6	90 ^c
11	Br	4-MeO	4-CO ₂ H	7	91 ^c

^aConditions: aryl halide (2 mmol), arylboronic acid (2.1 mmol), Na₂CO₃ (4 mmol), Pd catalyst (1.0 mol %), H₂O (10 mL), 100 °C. ^bYield after chromatographic separation (based on aryl halides, biphenyl yields in parentheses). ^cYield after recrystallization from ethanol–water.

catalyst charge, in sharp contrast to the reported 14% leaching of Pd/C catalyst.^{5c} No trace of coupled product was found by addition of the substrate, phenylboronic acid, and Na₂CO₃ to the filtrate after the brush was removed.

Tables 3 and 4 present examples demonstrating the scope of the reactions catalyzed by SiO₂-BisILsOct [PdEDTA]. All of the reactions proceeded under the conditions shown in Table 2, and were manipulated in air without any special precautions.

The results show that all of the reactions of aryl halides including aryl bromides and iodides with the arylboronic acids were carried out successfully in neat water. Aryl iodides were clearly more reactive; they gave the coupled products in yields ranging from 90% to almost 100% for the examples screened. Aryl bromides readily coupled with arylboronic acids under the reaction conditions employed and also gave high yields of coupled products, but the reaction time required was longer. Even chlorobenzene yielded the coupled product with PhB(OH)₂ in 66% yield when the reaction time was extended to 30 h. This yield is comparable to that reported previously wherein chlorobenzene gave a 65% yield under microwave irradiation conditions with 1 mol % of Pd/C.⁹ⁿ The catalyst also worked efficiently with heteroaryl halides such as 2-iodothiophene, 3-bromopyridine, and 3-iodopyridine (entries 14, 28, and 29, Table 3) as the coupling partners with high yields.

A broad range of functional groups can be tolerated in the reaction. Electron-withdrawing and electron-donating substituents on either the aryl halide or phenylboronic acid did not have a detrimental effect on the ability of the catalysts to promote this reaction to completion. The couplings proceeded successfully to give the desired products in high yields even in the presence of sensitive groups such as MeCO, CO₂H, NH₂, CN, and OH, without any protection. Similar to the Suzuki–Miyaura reactions reported previously, the aryl halides with electron-withdrawing groups gave higher yields than those with electron-donating substituents. Notably, 1-bromo-4-iodobenzene gave 4-bromodiphenyl in excellent yield when 1 equiv of phenylboronic acid was used, indicating that the reaction was highly selective.

It is particularly noteworthy that because of the solvent power of the immobilized ionic liquid, water-insoluble aryl halides were efficiently transformed to the desired products in excellent yield without the aid of organic cosolvent. The brush works well with solid aryl halides that do not melt at the reaction temperature. By contrast, most of the previously reported heterogeneous and homogeneous catalysts functioned efficiently only with water-soluble aryl halides,¹⁰ such as halobenzoic acids and halophenols; or they had to be used in organic solvent or water–organic mixed solvent if water-insoluble haloarylenes were used as the starting material.^{10f} Furthermore, all of the present reactions were carried out in neat water without the need for phase transfer catalyst and protection from air, showing that the methodology has distinct advantages.

In summary, we have developed an environmentally benign catalyst and procedure for Suzuki–Miyaura cross-coupling reactions. The catalyst combines the advantages of ionic liquid, PTC, and Pd catalyst together, and has proved to be highly efficient and recyclable for Suzuki reactions in water. Because of its recyclability and the use of neat water as the reaction medium it is distinguished by both green and economic advantages from other palladium-based catalysts. In addition to those features this catalytic system has the advantage of avoiding the need for inert gas and an organic cosolvent for water-insoluble aryl halides. In view of its simplicity and the mild conditions, the present protocol has been found to be a versatile and green route to diaryls in the laboratory, and could find industrial applications. Applications of this type of catalyst to other palladium-catalyzed reactions are in progress and will be reported in due course.

Experimental Section

1. Preparation of Catalyst (2 wt % Pd). A mixture of PdCl₂ (0.19 mmol, 0.034 g), Na₂EDTA (0.19 mmol, 0.071 g), and Na₂CO₃ (0.38 mmol, 0.040 g) in water (5 mL) was magnetically stirred at room temperature and pH 8–9 for 3 h. One gram of SiO₂-BisILsC₈H₁₅Cl and 5 mL of EtOH were added and the mixture was stirred for 12 h. The resulting yellowish powder was filtered, washed thoroughly with H₂O and EtOH, and dried

under vacuum. The catalyst is insensitive to air and moisture, and stable at room temperature.

2. General Procedure for the Suzuki Reaction. In air, aryl halide (2 mmol), phenylboronic acid (2.1 mmol, 0.256 g), Na₂CO₃ (4 mmol, 0.424 g), 10 mL of distilled water, and PdEDTA-brush catalyst were combined in a 50 mL round-bottomed flask. The reaction mixture was magnetically stirred and the temperature was maintained at 100 °C with an oil bath. Reaction progress was monitored by TLC. After reaction was completed, the reaction mixture was cooled to room temperature and ethyl acetate (20 mL) was added. The catalyst was separated by filtration, washed with EtOAc (3 × 5 mL) and water, and dried in vacuum. The combined organic layer was washed with saturated NaCl solution then dried with anhydrous MgSO₄, and the solvent was removed under reduced pressure to give crude product that was purified by silica gel column chromatography with petroleum ether–EtOAc as eluent.

3. Preparation of 4-Methoxybiphenyl. In air, a mixture of 4-bromoanisole (0.374 g, 2.0 mmol), phenylboronic acid (0.256 g, 2.1 mmol), Na₂CO₃ (0.424 g, 4 mmol), and the brush (0.104 g, 1.0 mol % of Pd) in 10 mL of H₂O was magnetically stirred and refluxed at 100 °C. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled to room temperature and ethyl acetate (20 mL) was added. The catalysts were separated by filtration, washed with EtOAc (3 × 5 mL) and water, and dried in vacuum. The combined organic layer was washed with saturated NaCl solution, dried with anhydrous MgSO₄, and concentrated under reduced pressure to give crude product that was purified by silica gel column chromatography with petroleum ether as eluent to produce 0.3662 g (99.5%) of 4-methoxybiphenyl. Mp 89–90 °C (recrystallized from EtOH); ¹H NMR (300 MHz, CDCl₃) δ 3.84 (s, 3H), 7.49 (m, 3H), 7.64–7.72 (m, 4H), 8.18–8.20 (d, *J* = 7.50 Hz, 2H).

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Supporting Information Available: Experimental procedures and spectral data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.